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# Clinical evidences of urea at high concentration on skin and annexes

Michela Starace | Aurora Alessandrini | Bianca Maria Piraccini

Department of Experimental, Diagnostic and Specialty Medicine-Division of Dermatology, University of Bologna, Bologna, Italy

**Correspondence**
Bianca Maria Piraccini, Department of Experimental, Diagnostic and Specialty Medicine-Division of Dermatology, University of Bologna, Bologna, Italy.
Email: biancamaria.piraccini@unibo.it

## Abstract

The antiproliferative, keratolytic, moisturizing and emollient properties of urea are already known. Clinical evidences of urea at high concentration indicate its important role in the presence of hyperkeratosis that, if severe or localized in specific body areas, may cause discomfort to the patient and may interfere with absorption of topical drugs, delaying response to treatment. Other important uses of urea at high concentration are on the scalp and on nail plate. The keratolytic effect of urea is well-tolerated and virtually free from side effects. Compliance with topical therapy is directly related to the aesthetic and sensory acceptability of a topical agent that may considerably vary in odour, spreadability and post-application residue.

## 1 | INTRODUCTION

Topical keratolytic agents are widely used in dermatology to debride scaling and as penetration enhancers of agents such as corticosteroids and antifungals. They work by dissolving intercellular matrix proteins and loosening the stratum corneum while simultaneously moisturizing the underlying epidermis.[1]

Urea is an ideal keratolytic with emollient and humectant properties. In particular, topical products containing urea at high concentration (40%-50%) are essential in the treatment of hyperkeratotic dermatoses and some nail disorders. Indeed, a large number of prescriptions for 40% and 50% urea products were written over the 3-year period 2004-2006 in the US.[2] Lower percentage of urea is used in the case of inflammatory skin disorders such as eczema, psoriasis or atopic dermatitis for its hydrating properties.[3]

The moisturizing effect of urea in dry and scaly skin conditions is widely studied and accepted.[4-7] Urea is known to exert a proteolytic, keratolytic, hydrating, hygroscopic, penetration-enhancing, epidermis-thinning, and antipruritic effect.[8-10] Furthermore, penetration enhancement for corticosteroids by urea is well studied.[11]

The purpose of this paper is to summarize the main uses of topical 40%-50% urea products in skin conditions (Table 1). In particular, we will focus on the most important conditions: psoriasis, dandruff and nail diseases.

## 2 | PSORIASIS

One of the main skin diseases that may benefit from the use of urea at high concentrations is reperesented by plaque psoriasis, that requires a lasting, stabilizing, and stage-adjusted treatment. Topical therapies in psoriasis are adequate in patients with limited plaques involving less than 20% of body surface area. A main component of this treatment in a holistic therapeutic concept consists of basic therapy with emollients and keratolytic agents in order to reduce scaling, itching, and subjective discomfort. Urea at 40%-50% is particularly useful for the treatment of localized hyperkeratotic plaques (Figure 1).[12-14] In a recent study, a 50% urea anhydrous paste applied twice a day in 25 patients with plaque psoriasis characterized by an evident hyperkeratotic component determined a clinical clearance of hyperkeratosis at day 21 in 92% of the treated plaques. An ultrasound significant reduction of the mean epidermal thickness score was also observed.[15] In psoriasis, urea may also been used to enhance the penetration of topically applied antipsoriatic drugs.[14]

## 3 | DANDRUFF

Scalp dandruff, a common condition generally resulting from seborrheic dermatitis (SD) and occasionally to scalp psoriasis (SP), is characterized by accumulation of scales, oily, red and flaky scalp,

  

often accompanied by itching. The most common treatment for thick scales, redness and flaky scalp resulting from SD or to SP is the use of shampoo formulations that most often contain keratolytic agents. Urea has antifungal and antimicrobial qualities and a keratolytic effect, as it loosens and softens scalps scales, making them easier to remove. Shemer et al published an article about scalp SD and SP treated with a 40% urea/1% bifonazole ointment. The study showed a benefit of the combination of urea and bifonazole over bifonazole alone by enhancing the bifonazole penetration. The authors reported that urea was able to reduce the plaque thickness.[16]

## 4 | NAIL DISEASES

Topical products containing 40%-50% urea are also extensively used for the treatment of nail diseases where its use is as a conservative method for softening nail plate and enhancing nail permeability, but also to enhance the penetration of drugs such as antimycotic agents. In the last few decades, creams, gels, lacquers and ointments containing high percentages of urea have been increasingly marketed for the treatment of different nail conditions characterized by nail thickening and hardening. Nail thickening is a common problem of the toenails, especially in elderly people, and it causes considerable cosmetic discomfort, since thickened nails are hard, difficult to trim, and often make wearing shoes painful. Nail thickening may be idiopathic, or secondary to other diseases ranging from onychomycosis to psoriasis,[17,18] onychogryphosis and pincer nails.[19] Urea at high concentrations induces nail softening and permits nail trimming or nail plate removal without irritation of the periungual tissues (Figures 2 and 3). When application is under occlusion, this effect is faster, inducing a rapid nail plate softing and easier absorption of drugs with a progressive chemical avulsion, resulting in a softer and more flexible nail plate. Urea induces a selective and gradual disintegration of corneocytes that starts in the superficial layers and gradually reaches the deep portions of the nail. The nail structure becomes grossly altered, with marked enlargement of the intercellular spaces.

In onychomycosis, the application of 40% urea cream is effective especially when nails are thickened[18] and/or uplifted and the patient complains of pain, spontaneous or when wearing shoes, with difficult walking. In these cases, the clinical improvement induced by systemic and topical antifungals appears very slowly, as the toenail growth rate is very low, about 1 mm/month. Elimination of the affected part of the nail plate is required to obtain healthy nail and patients often require podiatrist treatment in order to decrease foot pain and to walk properly. The application of 40% urea can induce nail plate maceration and softening, improving the subjective symptoms and increasing the penetration of active antifungals such as 1% bifonazole.[18]

**TABLE 1** Clinical uses of topical 40%-50% urea products

| |
|---|
| Psoriasis |
| Dandruff |
| Nail diseases (Onychomycosis, nail psoriasis,onychogriphosis) |
| Xerosis, Ichthyosis |
| Keratoderma |
| Eczema |
| Hyperkeratosis due to stasis dermatitis |
| Verruca vulgaris, corns or callosities |

## 5 | PATIENT'S COMPLIANCE AND SIDE EFFECTS

Patient's compliance in case of long-term treatment with topical products is an important aspect to consider: it is directly related to the aesthetic and sensory acceptability of the topical agent that may considerably vary in odour, spreadability and post-application residue.

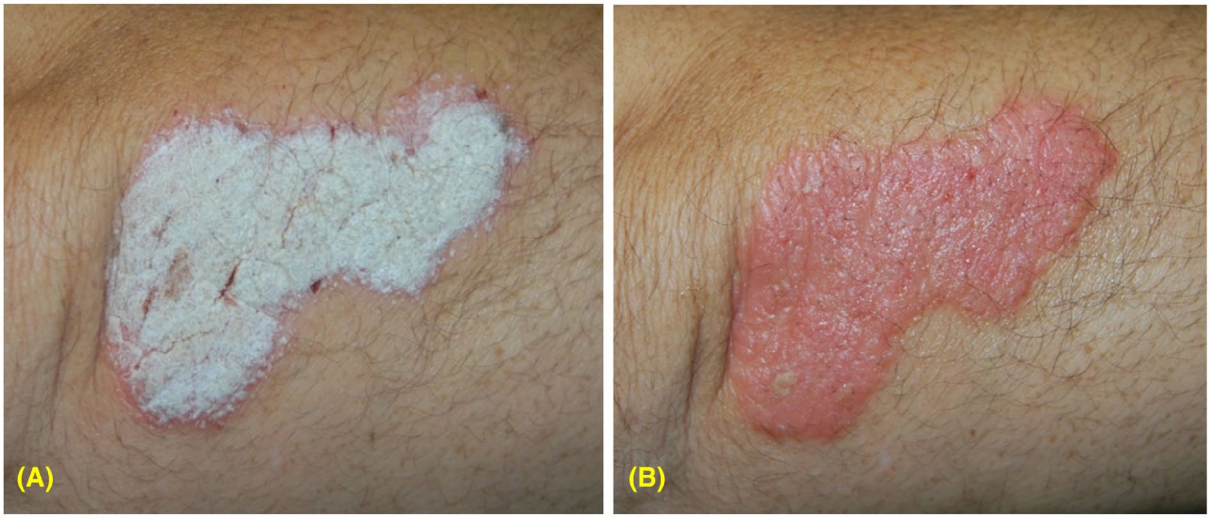


**FIGURE 1** Hyperkeratotic psoriatic plaque at baseline (A) and after 21 days of 50% urea cream


**FIGURE 2** Nail plate removal in pachyonychia: baseline (A) and after two cycles of 2-day application of 40% urea cream under occlusion


**FIGURE 3** Onychogriphosis at baseline (A) and after 4 days of 40% urea cream under occlusion

While ideal in theory, a challenging aspect of treating patients with urea products is overcoming their objections to smell, consistency, viscosity, colour, ease of application and post-application residue. Although a given topical therapy may perform well in clinical trials, patients may lose motivation to remain compliant when the topical preparation is difficult to apply or if it affects their personal

or professional lives in any negative way.[20] Simply put, if a topical therapy is unpleasant to a patient for whatever reason, he will likely not use it as prescribed.

Some of the limitations of these products, such as odour, excess residue on the skin and difficult application, may result in decreased compliance with therapy. Patients seek a product that is not only effective but also has minimal impact on their daily lives. Often, more "effective" preparations are far less tolerated by certain groups of patients. For example, ointments, despite enhancing drug delivery by improved penetration and occlusive properties, are often less tolerated than creams because of their greasy nature.[21] On the other hand, patients with dry, cracked hands and feet may welcome an ointment, although less spreadable.

All urea-based creams have a noticeable odour, because of volatile amine, but it dissipates quickly after application and is tolerated by the patients. In addition, because these products are typically used on the legs and feet (body areas that are far from the nose), this odour is rarely an objection to using urea preparations.[22]

In general, side effects of high concentration urea only include irritant cutaneous reactions, which are dose dependent and may be enhanced by occlusion.[23] In case of nail treatment, they may be seen when the product applied on the nail reaches the soft periungual skin. Allergic contact dermatitis represents a rare side effect.[24]

## 6 | CONCLUSION

In conclusion, urea at high concentration is widely utilized in topical products because of its moisturizing, keratolytic and antimicrobial properties. It is indicated in case of hyperkeratosis for its capacity of inducing an effective keratolytic action and its use is considered agreeable by all patients. When associated with pharmacological treatment, it speeds and enhances the absorption of the therapeutic drugs and their response. Side effects are rare and mainly include skin irritation.

### CONFLICT OF INTEREST

The authors do not have any conflict of interest to declare.

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